Message

From: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]
Sent: 6/3/2013 11:00:39 PM
To: tbstarr@mindspring.com
CC: Bussard, David [Bussard.David@epa.gov]; Perovich, Gina [Perovich.Gina@epa.gov]
Subject: RE: your msg

Hi Tom:

I hope you received my mail of Saturday. I am addressing the questions you sent last week (in blue within the body of your email below).

Best Regards,
Ravi.

From: tbstarr@mindspring.com
Sent: Wednesday, May 29, 2013 9:30 PM
To: Subramaniam, Ravi
Subject: Re: your msg

OK, Ravi, email it is. Here are 4 initial questions of clarification.

1. What specific dose-response function did you fit to the tumor data vs. total dG adducts in the nasal passages? I presume there were only 5 data points (0, 0.7, 2, 6, and 10 ppm) and that the tumor incidence and total adduct levels are those you described in the Appendix of your written comments to us, namely 4.7 at background, and then 4.7 added to the Lu et al. 2012 results for exogenous levels following single 6 hour exposures to the various formaldehyde air concentrations without any adjustments to equivalent steady-state.

Reproducing text from appendix sent to you earlier: These data are fit in Figure A6 with a multistage model with total adduct level for dose and constrained to include a linear term; $P(d) = 1-\exp(-a\cdot d-b\cdot d^{c})$, $a>0$, $b>0$, where d=total N2-hmdG adduct level. The value of the slope from the bottom up approach is $5.9\cdot10^{-5}$ whereas the slope of the multistage model fit to the tumor incidence at the background dose (mean endogenous adduct) is $1.1\cdot10^{-3}$ which is 19-fold higher.

Fig A6: Underestimation of slope of dose-response using bottom up approach. Bottom up slope (dashed line); Multistage model fit to tumor incidence data, highest dose deleted (solid line). Multistage model parameters: a= $1.7847\cdot10^{-8}$, b=$1.1421\cdot10^{-15}$, c=16.9983. Bottom panel: Axes truncated so that difference between curves at crossing point is visible.

Table A1: N2-hmdG Adduct levels (Lu et al 2011) and rat tumor data (Monticello et al. 1996, Subramaniam et al. 2007)

Exposure ppm	Mean Exogenous N2-hmdG (adducts /10^7 dG)	Total N2-hmdG (endogenous@ + exogenous) (adducts /10^7 dG)	Tumor Incidence
0	0	0	0
0	0	4.70	1/3602 = 0.00028
0.7	0.04	4.74	0/107
2.0	0.19	4.89	0/353
5.8	1.04	5.74	3/343=0.009

9.9*	2.26	6.96	22/103=0.214

@ The mean endogenous level of 4.7 adducts/10^7 dG as reported by Swenberg et al. (2011, Fig. 2) was used.

* 9.9 ppm was the concentration in the tumor bioassay. However, the adduct levels in Lu et al. 2011 were measured at 9.1 ppm therefore the exogenous adduct level was corrected with a linear extrapolation (value in Lu et al. is 2.02).

2. Were the coefficients of the linear and higher power term (and the power of dose) the only parameters of the dose-response model, and were they both allowed to vary? What, if any, constraints were imposed on the dose coefficients and the higher power of dose?

see above

3. What program did you use to optimize the function's parameters? Did you maximize the log-likelihood of the model conditional on the data? If you used a non-standard optimization program, can you provide me with the specific code you used? I would like to be able to replicate your results.

I used sigmaplot. I dont remember if it maximizes the log-likelihood.

4. Were you able to estimate an upper 95% confidence bound on the low-dose slope (slope at 4.7)?

I did not attempt that calculation because the purpose of the exercise was only illustrative and conclusions regarding underestimation would be conceptually similar if looking at upper bound estimates of risk instead.

Your answers may suggest additional questions of clarification.

If you have questions re my presentations, let me know what they are and I will do my best to answer them.

See email of Saturday AM.

Best regards,
Tom Starr